(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 341 990 A3**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 89304704.3

(51) Int. Cl.5: C07D 501/46, A61K 31/545

(22) Date of filing: 09.05.89

(30) Priority: 10.05.88 FR 88401143

(43) Date of publication of application:
15.11.89 Bulletin 89/46

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(88) Date of deferred publication of the search report:
15.05.91 Bulletin 91/20

(71) Applicant: IMPERIAL CHEMICAL INDUSTRIES PLC
Imperial Chemical House, Millbank
London SW1P 3JF(GB)

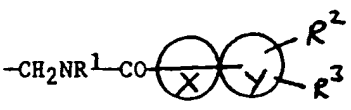
Applicant: I.C.I.- PHARMA
Immeuble "Le Galien", 1, Rue des Chauffours B.P. 127
F-95022 Cergy Cedex(FR)

(72) Inventor: Siret, Patrice Jean
9 Rue de Macon
F-51100 Reims(FR)
Inventor: Jung, Frederick Henri
Rue du Moulin Cilquot
Taissy F-51500 Rilly La Montagne(FR)
Inventor: Bell, William
57 Sycamore Crescent
Macclesfield Cheshire(GB)

(74) Representative: Denerley, Paul Millington, Dr. et al
Imperial Chemical Industries PLC Legal Department: Patents P.O. Box 6, Bessemer Road
Welwyn Garden City Hertfordshire AL7 1HD(GB)

(54) Cephalosporins, process for their preparation and pharmaceutical compositions.

(57) Cephalosporin antibiotics having a 3-position substituent of the formula:



are described, wherein R^1 is hydrogen or certain optionally substituted alkyl groups; X is a benzene ring or certain 5 or 6-membered heterocyclic ring and is fused to ring Y which is a nitrogen containing heteroaryl group; R^2 and R^3 are independently hydroxy or an in vivo hydrolysable ester thereof, and ring system X-Y is optionally substituted. Processes for their preparation and use are described.

EP 0 341 990 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 4704

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 265 185 (BEECHAM) * Pages 45-51; claims *	1-9	C 07 D 501/46 A 61 K 31/545
P,A	EP-A-0 267 733 (ICI PHARMA) * Pages 82-86; claims *	1-9	
P,A	EP-A-0 295 630 (HOFFMANN-LA ROCHE) * Pages 43-63; claims *	1-9	
P,A	EP-A-0 304 158 (IMPERIAL CHEMICAL INDUSTRIES) * Pages 64-78; claims *	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 501/00

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	05 March 91	LUYTEN H.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 341 990 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **09.11.94** (51) Int. Cl.5: **C07D 501/46**, A61K 31/545

(21) Application number: **89304704.3**

(22) Date of filing: **09.05.89**

(54) **Cephalosporins, process for their preparation and pharmaceutical compositions.**

(30) Priority: **10.05.88 FR 88401143**

(43) Date of publication of application:
15.11.89 Bulletin 89/46

(45) Publication of the grant of the patent:
09.11.94 Bulletin 94/45

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 265 185
EP-A- 0 267 733
EP-A- 0 295 630
EP-A- 0 304 158

(73) Proprietor: **IMPERIAL CHEMICAL INDUSTRIES PLC**
Imperial Chemical House,
Millbank
London SW1P 3JF (GB)

Proprietor: **ICI PHARMA**
Immeuble "Le Galien"
B.P. 127
1 Rue des Chauffours
F-95022 Cergy Cédex (FR)

(72) Inventor: **Siret, Patrice Jean**
9 Rue de Macon
F-51100 Reims (FR)
Inventor: **Jung, Frederick Henri**
Rue du Moulin Cliquot
Taissy F-51500 Rilly La Montagne (FR)
Inventor: **Bell, William**
57 Sycamore Crescent
Macclesfield Cheshire (GB)

(74) Representative: **Denerley, Paul Millington, Dr. et al**
ICI Group Patents Services Dept.
PO Box 6
Shire Park
Bessemer Road
Welwyn Garden City Herts, AL7 1HD (GB)

EP 0 341 990 B1

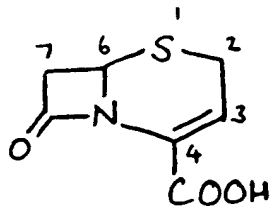
Description

The present invention relates to cephalosporins and in particular to such compounds comprising an amide group. This invention further relates to processes for their preparation, to intermediates in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are antibiotics and can be used in the treatment of any disease that is conventionally treated with antibiotics for example in the treatment of bacterial infection in mammals including humans. The compounds of this invention also have non-therapeutic uses as they can be used in conventional manner in industry for example they can be used as disinfectants and food preservatives. The compounds of this invention, however, are primarily of therapeutic interest as they show a desirable profile of activity and duration in their antibacterial effect.

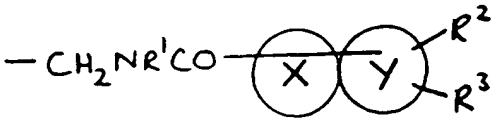
Investigation into new cephalosporin derivatives has been intense over the past 25 years with many thousands of patents and scientific papers having been published. A particular problem associated with the commercially available cephalosporins is the lack of potency against strains of Pseudomonas. The present invention provides cephalosporin derivatives having novel 3-position substituents, which derivatives possess good antibacterial activity and in particular against strains of Pseudomonas.

A further problem associated with many commercially available cephalosporins is the lack of stability to β-lactamase enzyme producing organisms and the consequent loss of antibacterial activity. The compounds of the present invention exhibit good stability to β-lactamase enzymes and thus are particularly useful in treating organisms that are β-lactamase producers.

The cephalosporin derivatives referred to herein are generally named in accordance with the 'cephem' nomenclature and numbering system proposed in J.A.C.S. 1962, 84,3400 and as depicted hereinbelow:



Accordingly the present invention provides a cephalosporin compound having a 3-position substituent of the formula (I):

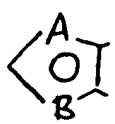


(I)

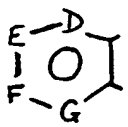
wherein:

R^1 is hydrogen, C_{1-6}alkyl optionally substituted by halo, hydroxy, C_{1-4}alkoxy, carboxy, amino, cyano, C_{1-6}alkanoylamino, phenyl or heteroaryl, or R^1 is C_{2-6}alkenyl;

X is a 5- or 6-membered ring selected from a group of the sub-formulae a) - b):



a)



b)

wherein A is CH or a nitrogen atom; B is oxygen, sulphur or a group NR^4; zero, one or two of D, E, F and G are nitrogen atoms and the remainder are CH groups: or X is a pyrazinone, pyridinone, pyridazinone or pyrimidinone ring, or is a thione equivalent of such a ring, said rings having a substituent R^4 on one nitrogen atom, or is pyranone, or pyranthione; the ring X being fused by any two adjacent carbon atoms to ring Y;

ring Y is a 6-membered heteroaryl ring containing one or two ring nitrogen atoms, substituted on adjacent carbon atoms by groups R^2 and R^3;

wherein either ring of the fused X-Y ring system is bonded via a carbon atom to the amide linkage;

R^2 is hydroxy or an in vivo hydrolysable ester thereof;

R^3 is ortho to R^2 and is hydroxy or an in vivo hydrolysable ester thereof;

R^4 is hydrogen, hydroxy, C_{1-6}alkoxy, phenoxy, C_{2-6}alkenyl or C_{1-6}alkyl, (any of these groups being optionally substituted by hydroxy, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, carboxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyloxy, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxycarbonylamino, phenyl, phenylC_{1-6}alkyl, carboxyaminocarbonyl, C_{1-6}alkoxycarbonyl-aminocarbonyl, benzoyl or C_{3-8}cycloalkyl) or R^4 is phenyl, C_{3-8}cycloalkyl, amino, C_{1-6}alkylamino or di-C_{1-6}alkylamino:

wherein the fused X - Y ring system and/or any phenyl group is optionally substituted by C_{1-6}alkyl, halo, hydroxy, hydroxy C_{1-6}alkyl, cyano, trifluoromethyl, nitro, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, C_{1-6}alkanoyl, C_{1-6}alkoxy, C_{1-6}alkylthio,C_{1-6}alkanoyloxy, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkyl carbamoyl, carboxy, carboxy C_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, sulpho, sulphoC_{1-6}alkyl, sulphonamido C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoylamino, thioureido or amidino.

In one aspect R^1 may be C_{1-6}alkyl substituted by heteroaryl. Suitably such a heteroaryl group is a 5- or 6-membered ring containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen and sulphur and may be optionally substituted, for example by the substituents described hereinbefore with respect to the fused X - Y ring system. For example R^1 may be pyridinylmethyl or furanylmethyl.

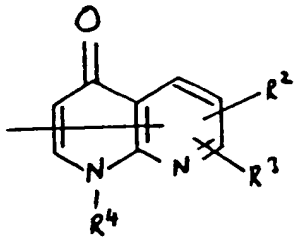
Particular meanings for R^1 are hydrogen, C_{1-6}alkyl for example methyl, ethyl or propyl, hydroxy C_{1-6}alkyl for example 2-hydroxyethyl, halo C_{1-6}alkyl for example 2-chloroethyl or 2-fluoroethyl, C_{1-6}alkoxy C_{1-6}alkyl for example 2-methoxyethyl, 2-ethoxyethyl or methoxymethyl, carboxy C_{1-6}alkyl for example carboxymethyl, phenyl C_{1-6}alkyl for example benzyl or phenethyl, or C_{2-6}alkenyl for example allyl.

Preferably R^1 is hydrogen, methyl or ethyl. Most preferably R^1 is hydrogen.

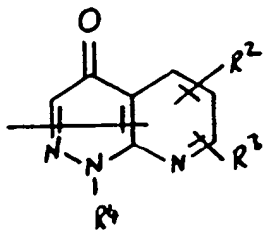
In one aspect X is a ring of the sub-formula a) as hereinbefore described, that is X is an imidazole, thiazole, oxazole, pyrrole, furan or thiophen ring.

In another aspect X is a ring of the sub-formula b) as hereinbefore described, for example benzene, pyridine, pyrimidine, pyrazine or pyridazine.

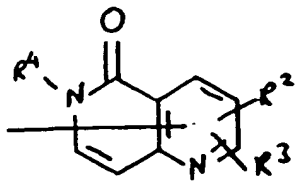
In a further aspect X is a pyrazinone, pyridinone, pyridazinone or pyrimidinone ring, or the thione equivalent of such rings, said rings having a substituent R^4 on one nitrogen atom. Y is a 6-membered heteroaryl ring containing either one or two ring nitrogen atoms, for example Y is pyridine, pyrimidine, pyrazine or pyridazine. For example the X - Y fused ring system may be of the sub-formula i)-x):



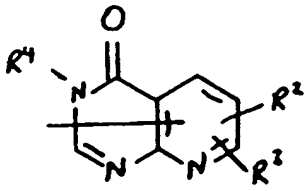
i)



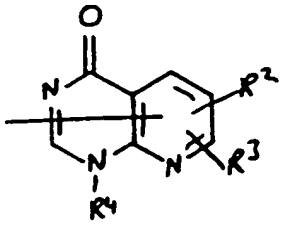
ii)



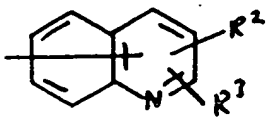
iii)



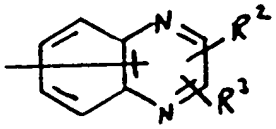
iv)



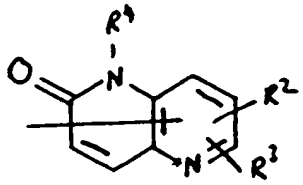
v)



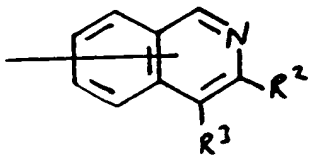
viii)



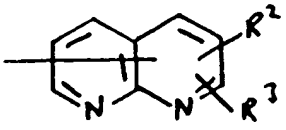
vii)



vi)



ix)



x)

Particular meanings of the group R^4 are hydrogen, C_{1-6}alkoxy for example methoxy or ethoxy, C_{1-6}alkyl for example methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl, C_{3-8}cycloalkyl for example cyclopropyl, hydroxy C_{1-6}alkyl for example hydroxymethyl or hydroxyethyl, phenyl or phenylC_{1-6}alkyl for example benzyl or phenethyl. Preferably R^4 is hydrogen, methoxy, ethoxy, methyl, ethyl or benzyl.

Preferred values for the X-Y fused ring system are those of the sub-formulae i) and v).

In another preferred aspect the X ring is a pyran-4-one ring. In alternative the X ring is a pyran-4-thione ring.

R^2 is hydroxy or an in vivo hydrolysable ester thereof. In vivo hydrolysable esters are those pharmaceutically acceptable esters that hydrolyse in the human or animal body to produce the parent hydroxy compound. Such esters can be identified by administering, e.g. intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters include C_{1-6} alkanoyloxy for example acetoxy, propionyloxy, pivaloyloxy, C_{1-4} alkoxycarbonyloxy for example ethoxycarbonyloxy, phenylacetoxy and phthalidyl.

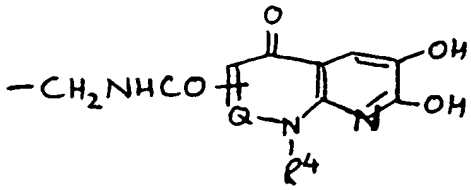
R^3 is hydroxy or an in vivo hydrolysable ester thereof.

Conveniently both R^2 and R^3 have the same value and are both hydroxy or are both in vivo hydrolysable esters, for example they are both acetoxy or pivaloyloxy.

For the avoidance of doubt, the amide group ($-CH_2NR^1CO-$) can be linked to either ring X or ring Y of the fused X-Y ring system. Substituents R^2 and R^3 are located on ring Y.

As stated hereinbefore the fused X-Y ring system may be optionally substituted on either ring. Particular substituents are C_{1-6} alkyl for example methyl or ethyl, halo for example chloro, fluoro or bromo, hydroxy, hydroxyC_{1-6} alkyl for example hydroxyethyl, amino, C_{1-6} alkylamino for example methylamino or ethylamino, di-C_{1-6} alkyl amino for example dimethylamino or diethylamino, C_{1-6} alkoxy for example methoxy or ethoxy, carboxy C_{1-6} alkyl for example carboxymethyl, C_{1-6} alkanoylamino for example acetamido, trifluoromethyl, carboxy, carbamoyl, C_{1-6} alkylcarbamoyl for example methylcarbamoyl, di-C_{1-6} alkylcarbamoyl for example dimethylcarbamoyl, C_{1-6} alkanoyl for example acetyl and C_{1-6} alkylthio for example methylthio.

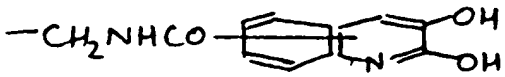
A favoured class of cephalosporin compounds of the present invention has a 3-position substituent of the formula (II):



(II)

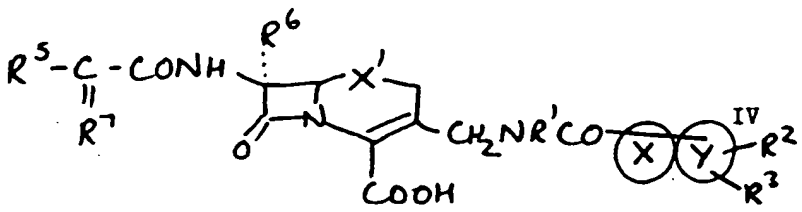
wherein Q is CH or N and R^4 is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy.

Another favoured class of cephalosporin compounds of the present invention has a 3-position substituent of the formula (III):



(III)

As stated hereinbefore the present invention relates to cephalosporins having a novel 3-position substituent. A particular class of cephalosporins within the present invention is that of the formula IV:-



IV

and salts and esters thereof wherein R^1-R^3, X and Y are as hereinbefore defined;

X^1 is sulphur, oxygen, methylene or sulphinyl;

R^6 is hydrogen, methoxy or formamido; and

R^5 and R^7 are groups known for such positions in the cephalosporin art.

Preferably X^1 is sulphur.

Preferably R^6 is hydrogen.

R^5 is for example 2-aminothiazol-4-yl or 2-aminooxazol-4-yl each optionally substituted in the 5-position by fluorine, chlorine or bromine, or R^5 is 5-aminoisothiazol-3- yl, 5-amino-1,2,4-thiadiazol-3-yl, 3-aminopyrazol-5-yl, 3-aminopyrazol-4-yl, 2-aminopyrimidin-5-yl, 2-aminopyrid-6-yl, 4-aminopyrimidin-2-yl, 2-amino-1,3,4-thiadiazol-5-yl or 5-amino-1-methyl-1,2,4-triazol-3-yl;

R^7 is for example of the formula $=N.O.R^8$ (having the syn configuration about the double bond) wherein R^8 is hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (1-3C)alkyl(3-6C)cycloalkyl, (3-6C)cycloalkyl(1-3C)-alkyl, (3-6C)alkenyl, optionally substituted by carboxy, (5-8C)cycloalkenyl, (3-6C)alkynyl, (2-5C)-alkylcarbamoyl, phenylcarbamoyl, benzylcarbamoyl, (1-4C)alkylcarbamoyl(1-4C)alkyl, di(1-4C)-alkylcarbamoyl(1-4C)alkyl, (1-4C)haloalkylcarbamoyl(1-4C)alkyl, (1-3C)haloalkyl, (2-6C)hydroxyalkyl, (1-4C)-alkoxy(2-4C)alkyl, (1-4C)alkylthio(2-4C)alkyl, (1-4C)alkanesulphinyl(1-4C)alkyl, (1-4C)alkanesulphonyl(1-4C)-alkyl, (2-6C)aminoalkyl, (1-4C)alkylamino(1-6C)alkyl, (2-8C)dialkylamino(2-6C)alkyl, (1-5C)cyanoalkyl, 3-amino-3-carboxypropyl, 2-(amidinothio)ethyl, 2-(N-aminoamidinothio)ethyl, tetrahydropyran-2-yl, thietan-3-yl, 2-oxopyrrolidinyl, or 2-oxotetrahydrofuranyl, or R^8 is of the formula V:-

$$-(CH_2)_q-C(COOH)=CR^9R^{10} \qquad (V)$$

wherein q is one or two and R^9 and R^{10} are independently hydrogen or C_{1-4}alkyl; or R^8 is of the formula VI:-

$$-CR^{11}R^{12}-(CH_2)_r-COR^{13} \qquad VI$$

wherein r is 0-3, R^{11} is hydrogen, (1-3C)alkyl or methylthio, R^{12} is hydrogen, (1-3C)alkyl, (3-7C)cycloalkyl, cyano, carboxy, (2-5C)carboxyalkyl or methanesulphonylamino, or R^{11} and R^{12} are joined to form, together with the carbon to which they are attached, a (3-7C)carbocyclic ring, and R^{13} is hydroxy, amino, (1-4C)-alkoxy, (1-4C) alkylamino or of the formula $NHOR^{14}$ in which R^{14} is hydrogen or (1-4C)alkyl;

or R^7 may be of the formula $=CH.R^{15}$ wherein R^{15} is hydrogen, halogen, (1-6C)alkyl, (3-7C)cycloalkyl, (2-6C)alkenyl, (3-7C)cycloalkenyl, phenyl or benzyl.

Particular meanings for R^8 are hydrogen, methyl, ethyl, isopropyl, t-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclopropyl, methylcyclobutyl, methylcyclopentyl, methylcyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, allyl, cyclopentenyl, cyclohexenyl, propargyl, methylcarbamoyl, ethylcarbamoyl, phenylcarbamoyl, benzylcarbamoyl, 2-chloroethyl, 2-fluoroethyl, 2-bromoethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 2-ethoxyethyl, 2-methylthio-ethyl, 2-methanesulphinylethyl,2- methanesulphonyl-ethyl, 2-aminoethyl, 3-aminopropyl, 2-methylamino ethyl, 2-dimethylaminoethyl, cyanomethyl, 2-cyanoethyl, azidomethyl, 2-azidoethyl, ureidomethyl, 3-amino-3-carboxypropyl, 2-(amidino)ethyl, 2-(N-aminoamidino)-ethyl, tetrahydropyran-2-yl, thietan-3-yl, 2-oxopyrrolidinyl and 2-oxo-tetrahydrofuran-3-yl,

or, when R^8 is of the formula V in which q is 1 or 2, a particular meaning for R^8 is when R^9 and R^{10} are hydrogen or methyl,

or, when R^8 is of the formula VI, a particular meaning for R^8 is when $r=0$ and R^{11} is hydrogen, methyl or methylthio, R^{12} is hydrogen, methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyano, carboxy, carboxymethyl, 2-carboxyethyl or methanesulphonylamino, or when R^{11} and R^{12} are joined to form, together with the carbon to which they are attached, a cyclopropane, cyclobutane, cyclopentane, cyclohexane or cycloheptane ring and R^{13} is hydroxy, amino, methoxy, ethoxy, methylamino, ethylamino, or of the formula $NHOR^{14}$ in which R^{14} is hydrogen, methyl or ethyl.

Preferably R^8 is C_{1-6}alkyl for example methyl or ethyl, 1-carboxycyclobutyl, 1-carboxycyclopentyl, or 2-carboxyprop-2-yl. In particular R^8 is 2-carboxyprop-2-yl.

Particular meanings for R^{15} are hydrogen, methyl, ethyl or chlorine.

The cephalosporin derivatives referred to herein are generally named in accordance with the 'cephem' nomenclature and numbering system proposed in J.A.C.S. 1962, 84,3400.

A particularly preferred class of cephalosporins of the present invention is that wherein R^5 is 2-aminothiazol-4-yl, R^7 is a group $=NOR^8$ wherein R^8 is C_{1-6}alkyl, 1-carboxycyclobutyl, 1-carboxycyclopentyl or 2-carboxyprop-2-yl, R^6 is hydrogen, X^1 is sulphur and the 3-position substituent is of the formula (II) or (III).

It should be realised, of course, that the present invention covers all tautomeric forms, for example the sub-formulae i)-vi) are depicted in the keto form; where possible these may exist and be depicted in the

enol form. Such tautomers are, of course, within the scope of the present invention. Furthermore, where possible, the X ring may be optionally substituted by hydroxy and this may exist in the tautomeric keto form. In addition the groups R^2 and R^3 may be hydroxy and may exist, where possible, in the tautomeric keto form.

As stated hereinbefore the compounds of this invention ar primarily intended for use in therapy. Therefore in a preferred aspect the present invention provides a cephalosporin compound having a 3-position substituent of the formula I or a pharmaceutically acceptable salt or ester thereof. Suitable salts include acid addition salts such as hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine or N,N-dibenzylethylamine.

In order to use a compound of the present invention or a pharmaceutically acceptable salt or ester thereof for the therapeutic treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a cephalosporin compound having a 3-position substituent of the formula I or a pharmaceutically acceptable salt or ester thereof and a pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes it may be formulated by means known to the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, emulsions, dispersible powders, suppositories and sterile injectable aqueous or oily solutions or suspensions.

In addition to the pharmaceutically acceptable cephalosporin derivative of the present invention the pharmaceutical composition of the invention may also contain, or be co-administered with, one or more known drugs selected from other clinically useful antibacterial agents (for example other beta-lactams or aminoglycosides), inhibitors of beta-lactamase (for example clavulanic acid), renal tubular blocking agents (e.g. probenicid) and inhibitors of metabolising enzymes (for example inhibitors of peptidases, for example Z-2-acylamino-3-substituted propenoates).

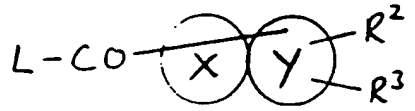
A preferred pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection, for example a sterile injectable containing between 1 and 50% w/w of the cephalosporin derivative, or one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100 mg. and 1 g. of the cephalosporin derivative.

The pharmaceutical compositions of the invention will normally be administered to man in order to combat infections caused by bacteria, in the same general manner as that employed for cephalothin, cefoxitin, cephradine, ceftazidime and other known clinically used cephalosporin derivatives, due allowance being made in terms of dose levels for the potency of the cephalosporin derivative of the present invention relative to the known clinically used cephalosporins. Thus each patient will receive a daily intravenous, subcutaneous or intramuscular dose of 0.05 to 30 g., and preferably 0.1 to 10 g., of the cephalosporin derivative, the composition being administered 1 to 4 times per day, preferably 1 or 2 times a day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose. Thus a preferred daily oral dose is 0.5 to 10 g. of the cephalosporin derivative, the composition being administered 1 to 4 times per day.

In a further aspect the present invention provides a process for preparing a cephalosporin compound having a 3-position substituent of the formula I, which process comprises:

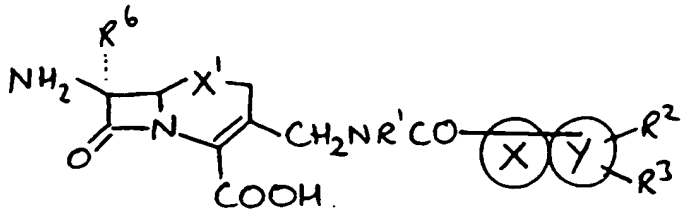
a) reacting a cephalosporin compound having a 3-position substituent of the formula:

$-CH_2NHR^1$ wherein R^1 is as hereinbefore defined with a compound of the formula VII:

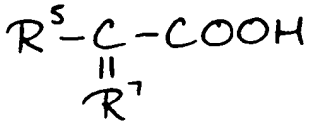


VII

wherein X, Y, R^2 and R^3 are as hereinbefore defined and L is a leaving group; or
b) for compounds of the formula IV, reacting a compound of the formula VIII with a compound of the formula IX or a reactive derivative thereof:

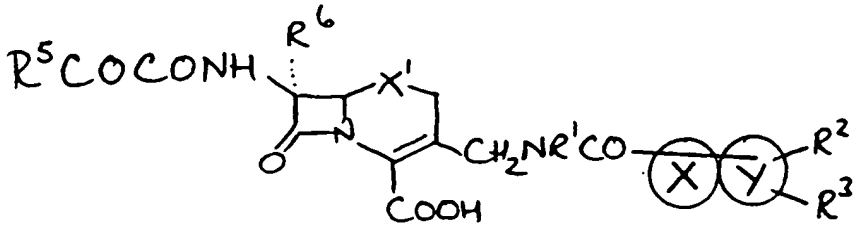


VIII



IX

wherein R^1, R^2, R^3, X^1, X, Y, R^5, R^6 and R^7 are as hereinbefore defined; or
c) for compounds of the formula IV wherein R^7 is a group $=NOR^8$, reacting a compound of the formula X:



(X)

wherein R^1, R^2, R^3, R^5, R^6, X^1, X and Y are as hereinbefore defined, with a compound of the formula: R^8ONH_2 wherein R^8 is as hereinbefore defined; or
d) for compounds of the formula IV wherein R^7 is a group $=NOR^8$ and R^8 is other than hydrogen, reacting a compound of the formula IV as hereinbefore defined wherein R^7 is a group $=NOH$ with a compound of the formula XI:

$L^1 - R^{16}$ XI

wherein L^1 is a leaving group and R^{16} is a group R^8 other than hydrogen; or
e) for compounds of the formula IV forming a group R^5 by cyclizing an appropriate precursor thereof:
wherein any functional groups are optionally protected:
and thereafter, if necessary:
i) removing any protecting group,
ii) for preparing in vivo hydrolysable esters, esterifying corresponding hydroxy groups,
iii) converting compounds wherein X^1 is S to compounds wherein X^1 is sulphinyl and vice versa,
iv) forming a pharmaceutically acceptable salt.

In the reaction between a cephalosporin compound having a 3-position substituent of the formula: $-CH_2NHR^1$ and a compound of the formula VII, conveniently L is a leaving group such as halo for example chloro, bromo or iodo. Most suitably the reaction is performed under conditions conventional for the reaction of acid halides with amines for example in the presence of an organic amine such as triethylamine. Suitably the reaction is performed at an ambient or lower temperature in a substantially inert solvent such as dimethylformamide and/or dichloromethane. In an alternative aspect the leaving group L is part of an activated ester formed with the acid precursor of the compound of the formula VII, i.e. a compound wherein L is -OH provides an activated ester, e.g. dicyclohexylcarbodi-imide provides an activated ester of the formula VII wherein L is $-OC(NHC_6H_{11})=NC_6H_{11}$, which group is displaced by the cephalosporin having a 3-position substituent of the formula: $-CH_2NHR^1$. Formation and reaction of the active ester is performed in conventional manner in the presence of reaction promotors such as hydroxybenzotriazole and triethylamine, for example in a substantially inert organic solvent such as dimethylformamide at a non-extreme temperature such as 10°C-50°C.

The cephalosporin starting-materials for this reaction are known from the art, or are made by methods analogous to those of the art. See for example EP-A-127992 and EP-A-164944.

The compounds of the formula VII are either known in the art or are made by methods analogous thereto. For example compounds wherein L is chloro are conveniently prepared from the corresponding acids. The acids are known or are prepared by methods of heterocyclic chemistry known to those skilled in the art, for example as in the hereinafter described Examples.

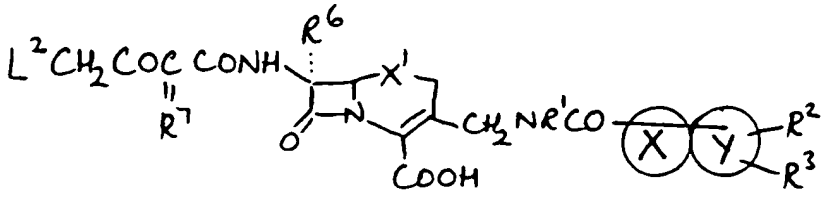
The reaction between compounds of the formulae VIII and IX is performed under conditions conventional in the cephalosporin art, for example under standard acylation conditions wherein for example the acid is activated as an acid bromide, acid chloride, anhydride or activated ester, or the reaction is performed in the presence of a coupling reagent such as dicyclohexylcarbodi-imide.

The compounds of the formula VIII can be prepared in a manner analogous to that described for the compounds having the 3-substituent of the formula I, with the 7-amino group being optionally protected.

The reaction between compounds of the formula X and R^8ONH_2 is performed under conditions standard in the general chemical and/or cephalosporin art. The compounds of the formula X can be prepared in a manner analogous to that described for the compounds having the 3-substituent of the formula I.

The reaction between the compound of the formula IV wherein R^7 is a group =NOH and a compound of the formula XI is performed under conditions standard in the general chemical and/or cephalosporin art.

A group R^5 may be formed by cyclizing an appropriate precursor. For example compounds of the formulae XII and XIII:



(XII)

NH_2CSNH_2 (XIII)

wherein R^7, R^6, X^1, R^1, R^2, R^3, X and Y are as hereinbeforedefined and L^2 is a leaving group, may be reacted to form a 2-aminothiazol-4-yl group. A nitrogen atom of the thiourea may be optionally protected during this cyclization.

The compounds of the formula XII can be prepared in a manner analogous to that described for the compounds of the formula I.

The compounds of the formulae IX, XI and R^8ONH_2 are known from, or can be made by the methods of, the general chemical and/or cephalosporin art.

The compounds of the formulae VIII, X and XII are novel and as such form a further aspect of the present invention.

In the process of this invention any functional group can be optionally protected, if appropriate. Such protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question, and may be introduced by conventional methods.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxyl protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming phenol, silanol or stannanol (the said alcohol, phenol, silanol or stannanol preferably containing 1-20 carbon atoms).

Examples of carboxyl protecting groups include straight or branched chain (1-12C)alkyl groups (eg isopropyl, t-butyl); halo lower alkyl groups (eg 2-iodoethyl, 2,2,2-trichloroethyl); lower alkoxy lower alkyl groups (eg methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (eg acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (eg 1-methoxy-carbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (eg p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (eg trimethylsilyl and t-butyldimerthylsilyl); tri(lower alkyl)silyl lower alkyl groups (eg trimethylsilylethyl); and (2-6C)alkenyl groups (eg allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxyl protecting groups include lower alkanoyl groups (eg acetyl); lower alkoxycarbonyl groups (eg t-butoxycarbonyl); halo lower alkoxycarbonyl groups (eg 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkylsilyl (eg trimethylsilyl, t-butyldimethylsilyl) and aryl lower alkyl (eg benzyl) groups. In addition two hydroxy groups substituted on adjacent carbon atoms, for example in the catechol moiety, may be protected in the form of a cyclic acetal such as the methylenedioxy moiety.

Examples of amino protecting groups include formyl, aralkyl groups (eg benzyl and substituted benzyl, eg p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; acyl (eg alkoxycarbonyl and aralkoxycarbonyl eg t-butoxycarbonyl and benzyloxycarbonyl); trialkylsilyl (eg trimethylsilyl and t-butyldimethylsilyl); alkylidene (eg methylidene); benzylidene and substituted benzylidene groups; and the phthalimido group.

The following biological test methods, data and Examples serve to illustrate this invention.

Antibacterial Activity

The pharmaceutically acceptable cephalosporin compounds of the present invention are useful antibacterial agents having a broad spectrum of activity in vitro against standard laboratory microorganisms, both Gram-negative and Gram-positive, which are used to screen for activity against pathogenic bacteria. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system. The compounds have particularly high activity in vitro against strains of Pseudomonas aeruginosa.

The antibacterial properties of the compounds of the invention may also be demonstrated in vivo in conventional mouse protection tests.

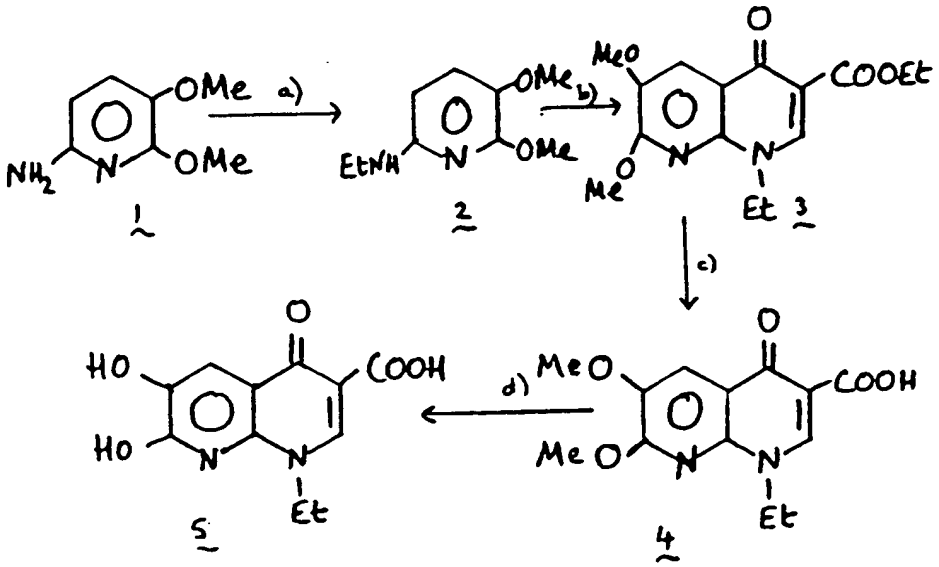
Cephalosporin derivatives have generally been found to be relatively non-toxic to warm-blooded animals, and this generalisation holds true for the compounds of the present invention. Compounds representative of the present invention were administered to mice at doses in excess of those required to afford protection against bacterial infections, and no overt toxic symptoms or side effects attributable to the administered compounds were noted.

The following results were obtained for representative compounds on a standard in vitro test system using Isosensitest agar medium. The antibacterial activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot.

ORGANISM	MIC (µl/ml)	
	EXAMPLE	
	1	2
P.aeruginosa PU21 (A8101028)	0.008	0.06
Ent. cloacae P99 (A8401054)	0.015	0.03
Serr.marcesens (A8421003)	0.008	0.008
Pr.morganii (A8433001)	0.008	0.008
Kleb.aerogenes (A8391027)	0.008	0.008
E. coli DCO (A8341098)	0.008	0.008
St.aureus 147N (A8601052)	16	2
S.dublin (A8369001)	0.008	0.008
Strep.pyogenes (A681018)	0.5	0.06

Example 1

7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-2-carboxamidomethyl)ceph-3-em-4-carboxylicacid.



a) To compound 1 (6g) (Clark et al., Aust. J. Chem. 1981, 34, 927) in methanol (100ml), at 0°C, was added sodium cyanoborohydride (2.67g) and acetaldehyde (2.6ml) at a pH of 5 maintained with methanolic hydrochloric acid. The solution was stirred for 90 minutes at room temperature and evaporated to give a residue which was dissolved in ether, washed with water and evaporated to give compound 2 (6g); NMR ($CDCl_3$) 1.45(t,3H); 3.2(dd,2H); 3.75(s,3H); 3.9(s,3H); 5.8(d,1H); 6.95(d,1H).

b) Compound 2 (6g) and ethoxymethylene malonate (6.6ml) were heated at 120°C for 1 hour. The crude oil was stirred in pentane, evaporated and cyclized with polyphosphoric ester (100g) at 100°C for 45 minutes. The mixture was cooled, poured on to ice; the aqueous phase was washed with ether, the pH adjusted to 8 and extracted into ethyl acetate. The solvent was evaporated to give a black solid that was triturated under ether to give compound 3 (3.4g); NMR ($CDCl_3$) 1.25-1.7 (m,6H); 3.95(s,3H); 4.1(s,3H);

4.2-4.5(m,4H); 8(s,1H); 8.45(s,1H).

c) Compound 3 (3.3g) in ethanol (10ml) and 2N sodium hydroxide (20ml) was heated under reflux for 90 minutes. Ethanol was evaporated, the aqueous phase acidified to pH2 and the resultant precipitate collected by filtration. Chromatography on silica, eluting with dichloromethane-methanol (98:2) gave compound 4 (1.3g); NMR (DMSO-d_6/CF_3COOD) 1.25-1.5(m,3H); 3.9(s,3H); 4.05(s,3H); 4.3-4.7(m,2H); 7.8-(s,1H); 8.95(s,1H).

d) Compound 4 (1.3g) and boron tribromide (5ml) were stirred in dichloromethane (10ml), at room temperature for 3 hours. The solvent was evaporated and the residue hydrolysed by slow addition to ice. The pH was adjusted to 2-3 and the resultant precipitate was collected and purified by chromatography on HP20SS resin (eluting with methanol:water:1% acetic acid (40:60)) (drying by azeotropic distillation using benzene) to give compound 5 (500mg); NMR (DMSO-d_6/CF_3COOD/CD_3COOD) 1.25-1.5 (m,3H); 4.4-4.7(m,2H); 7.2(s,1H); 8.85(s,1H).

e) Compound 5 (250mg), hexamethyldisilazane (1.26ml) and saccharin (20mg) were stirred under reflux in chloroform (10ml) for 2 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (5ml), cooled to -10°C, and triethylamine (1.55µl) and thionyl chloride (80µl) were added. The mixture was stirred for 30 minutes at room temperature and then added to 3-aminomethyl-7-[2-(2-aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]ceph-3-em-4-carboxylic acid (484mg) in dimethylformamide (5ml) in the presence of triethylamine (700µl), at 0°C, for 15 minutes. The solvent was evaporated and the residue purified over HP20 resin (eluting with methanol-water-1% acetic acid (70:30)) to give the product cephalosporin (130mg); NMR (DMSO-d_6/CF_3COOD/CD_3COOD) 1.25-1.5(m,3H); 1.5(s,6H); 3.5-3.7(m,2H); 3.9-4.6(m,4H); 5.15(d,1H); 5.8(d,1H); 7, 7.65 and 8.6 (3s,3H).

Example 2

7-[2-(2-Aminothiazol-4-yl)-2-((Z)-ethoxyimino)acetamido]-3-(1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-2-carboxamidomethyl)ceph-3-em-4-carboxylic acid.

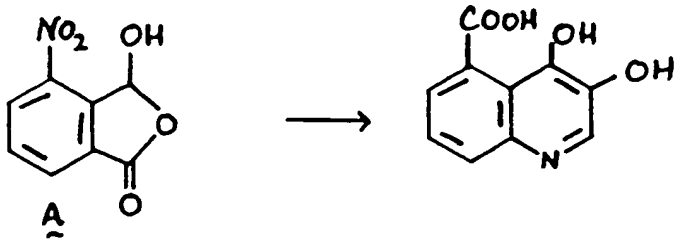
To compound 5 (from Example 1) (160mg) was added trimethylsilyl chloride (480µl) and triethylamine (630µl) in chloroform (10ml). The mixture was stirred under reflux for 90 minutes, cooled to 0°C and thionyl chloride (102µl) and triethylamine (196µl) were added. The mixture was stirred at room temperature for 30 minutes, evaporated and added to a solution of 3-aminomethyl-7-[2-(2-aminothiazol-4-yl)-2-((Z)-ethoxyimino)acetamido]ceph-3-em-4-carboxylic acid (270mg) in dimethylformamide (10ml) in the presence of triethylamine (440µl). This mixture was stirred at 0°C for 15 minutes, evaporated and purified over HP20 resin (eluting with methanol:1% acetic acid (70:30)) to give the product cephalosporin (100mg); NMR (DMSO-d_6/CF_3COOD/CD_3COOD) 1.25-1.5(m,6H); 3.2-3.8(m,2H); 4.0-4.7(m,6H); 5.15(d,1H); 5.75(d,1H); 7.0-(s,1H); 7.65(s,1H); 8.7(s,1H).

Example 3

7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido-3-(3,4-dihydroxyquinoline-5-carboxamidomethyl)ceph-3-em-4-carboxylic acid.

To a solution of 3,4-dihydroxyquinoline-5-carboxylic acid (51mg) in chloroform (5ml) and triethylamine (0.207ml) was added trimethylsilyl chloride (0.19ml). The mixture was heated at 55-60°C for 5 hours, cooled and treated, successively, with triethylamine (0.038ml) and thionyl chloride (0.020ml). After 30 minutes the mixture was added to 3-aminomethyl-7-[2-(2-aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]ceph-3-em-4-carboxylic acid (120mg) in methanol (10ml) containing triethylamine (0.14ml) at 0°C. The mixture was stirred for 1 hour at 0°C, diluted with water, acidified to pH2 and concentrated under reduced pressure. The residue was subjected to chromatography on HP20SS resin to give the title compound (27mg); NMR (DMSO-d_6/CD_3COOD/CF_3COOD) 1.55(s,6H); 3.70(m,2H); 4.40(m,2H); 5.25(d,1H); 5.85(d,1H); 7.10(s,1H); 7.55(d,1H); 7.80(t,1H); 8.0(d,1H); 8.5(s,1H).

The quinoline carboxylic acid was obtained as follows:-



Compound A (2.5g) in ethanol (50ml) was hydrogenated, for 90 minutes, at atmospheric pressure over 10% palladium on charcoal (250mg). The mixture was filtered and concentrated to about 10ml by heating at 40°C under reduced pressure.

In another flask, potassium cyanide (1.5g) was added to 1M sodium carbonate solution (50ml). Nitrogen was bubbled through the solution for 30 minutes, glyoxal bisulphite (4.15g) added and the product of the hydrogenation described above. The mixture was stirred for 2.5 hours, acidified to pH2 with 6N HCl and the resultant solid was collected by filtration, washed and dried to give 3,4-dihydroxyquinoline-5-carboxylic acid (770mg); MS (EI): 205($M^{+}\cdot$), 187 $(M-H_2O)^{+}\cdot$, 161 $(M-CO_2)^{+}\cdot$.

Example 4

7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(2,3-dihydroxyquinoline-4-carboxamidomethyl)ceph-3-em-4-carboxylic acid.

Trimethylsilylchloride (191µl, 1.5mM) was added to a stirred suspension of 4-carboxy-3-hydroxyquinol-2-one (51mg, 0.25mM) in chloroform (2ml) under an atmosphere of argon, triethylamine was then added 208µl, 1.5mM) and the mixture left to stir for 30 minutes. Thionyl chloride (20µl, 0.275mM), triethylamine (38µl, 0.275mm) and dimethylformamide (2-4µl:catalytic amount) were added in succession and the reaction mixture left to stir for 1.5 hours. This solution was then added quickly via a syringe to a cooled (ice/water bath) solution of silylated 3-aminomethyl-7-[2-(2-aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]ceph-3-em-4-carboxylic acid under an atmosphere of argon, left to stir for 15 minutes at 0°C and then for 90 minutes at room temperature. Solvent was removed by evaporation and the residue was triturated with water (10ml) and the precipitate collected by filtration to give the crude product (280mg), which was purified by HPLC on silica (C18) eluting with acetonitrile/water/trifluoroacetic acid (22.5/77.5/0.1) to give the title compound (70mg); NMR ($DMSOd_6/CF_3COOD$) 1.49(s,3H); 1.51(s,3H); 3.54-(d,1H); 3.72(d,1H); 4.17 and 4.23(dd,1H); 4.50 and 4.58(dd,1H); 5.19(d,1H); 5.86 and 5.84(dd,1H); 7.06(s,1H); 7.09-7.2(m,1H); 7.2-7.4(m,3H); 8.79(t,1H); 9.70(d,1H).

Example 5

7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(2,3-dihydroxyquinoline-8-carboxamidomethyl)ceph-3-em-4-carboxylic acid.

To a solution of 3-hydroxy-8-carboxy-2(1H)-quinolinone (160mg) in chloroform (15ml) was added triethylamine (0.62ml) and speedily trimethylsilyl chloride (0.57ml). The mixture was heated to 60°C for 4 hours, cooled to 0°C and treated with triethylamine (0.114ml) and thionyl chloride (0.06ml), whereupon the resultant solution was stirred for 2 hours at 0°C and at room temperature for 30 minutes. This solution was added to 3-aminomethyl-7-[2-(2-aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]ceph-3-em-4-carboxylic acid (360mg) in methanol (30ml) containing triethylamine (0.42ml) at 0°C. The reaction mixture was stirred for 30 minutes at 0°C, stirred for 30 minutes at room temperature, diluted with water, acidified to pH2, concentrated, and purified by chromatography (HP20SS resin eluting with methanol/water/acetic acid) to give the title compound (85mg); NMR ($DMSO-d_6/CD_3COOD/CF_3COOD$) 1.50(s,6H); 3.55(m,2H); 4.40(m,2H); 5.1(d,1H); 5.75(d,1H); 7.00-7.25(,3H); 7.6(d,1H); 7.80(d,1H).

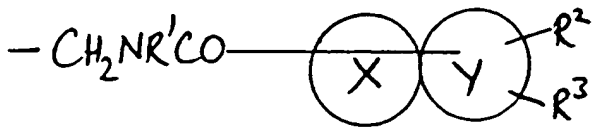
The starting material was obtained as follows:

A suspension of 7-methoxycarbonylisatin (2.4g) in ether (50ml) was treated at -5°C with a solution of

diazomethane (1.5g) in ether (140ml). The mixture was stirred for 3 hours and acetic acid (3ml) added. The mixture was filtered and the filtrate concentrated under reduced pressure to give a residue that was purified by column chromatography (silica gel eluting with dichloromethane/methanol) to give 3-hydroxy-8-methoxycarboxy-2-(1H)-quinolinone (350mg). This in methanol (10ml) was treated with 2N sodium hydroxide (1.75ml) at room temperature for 2.5 hours. The mixture was acidified with 2N HCl and the precipitate was collected and dried to give 3-hydroxy-8-carboxy-2(1H)-quinolinone (180mg); NMR (DMSO-d_6/CF_3COOD) 7.12-7.30(m,2H); 7.75(d,1H); 8.01(d,1H).

Claims

1. A cephalosporin compound having a 3-position substituent of the formula (I):

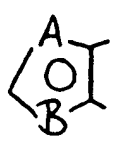


(I)

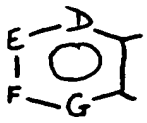
wherein:

R^1 is hydrogen, C_{1-6}alkyl optionally substituted by halo, hydroxy, C_{1-4}alkoxy, carboxy, amino, cyano, C_{1-6}alkanoylamino, phenyl or heteroaryl, or R^1 is C_{2-6}alkenyl;

X is a 5- or 6-membered ring selected from a group of the sub-formulae a) - b):



a)



b)

wherein A is CH or a nitrogen atom; B is oxygen, sulphur or a group NR^4; zero, one or two of D, E, F and G are nitrogen atoms and the remainder are CH groups: or X is a pyrazinone, pyridinone, pyridazinone or pyrimidinone ring, or is a thione equivalent of such a ring, said rings having a substituent R^4 on one nitrogen atom, or is pyranone, or pyranthione; the ring X being fused by any two adjacent carbon atoms to ring Y;

ring Y is a 6-membered heteroaryl ring containing one or two ring nitrogen atoms, substituted on adjacent carbon atoms by groups R^2 and R^3;

wherein either ring of the fused X-Y ring system is bonded via a carbon atom to the amide linkage;

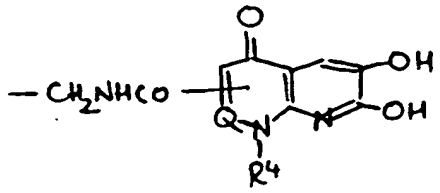
R^2 is hydroxy or an in vivo hydrolysable ester thereof;

R^3 is ortho to R^2 and is hydroxy or an in vivo hydrolysable ester thereof;

R^4 is hydrogen, hydroxy, C_{1-6}alkoxy, phenoxy, C_{2-6}alkenyl or C_{1-6}alkyl, (any of these groups being optionally substituted by hydroxy, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, carboxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyloxy, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxycarbonylamino, phenyl, phenylC_{1-6}alkyl, carboxyaminocarbonyl, C_{1-6}alkoxycarbonylaminocarbonyl, benzoyl or C_{3-8}cycloalkyl) or R^4 is phenyl, C_{3-8} cycloalkyl, amino, C_{1-6}alkylamino or di-C_{1-6}alkylamino: wherein the fused X-Y ring system and/or any phenyl group is further optionally substituted by C_{1-6}alkyl, halo, hydroxy, hydroxy C_{1-6}alkyl, cyano, trifluoromethyl, nitro, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, C_{1-6}alkanoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoyloxy, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkyl carbamoyl, carboxy, carboxy C_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, sulpho, sulphoC_{1-6}alkyl, sulphonamido C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoylamino, thioureido or amidino.

2. A compound according to claim 1 wherein R^2 and R^3 are both hydroxy.

3. A compound according to claim 1 wherein the cephalosporin compound has a 3-position substituent of the formula (II):



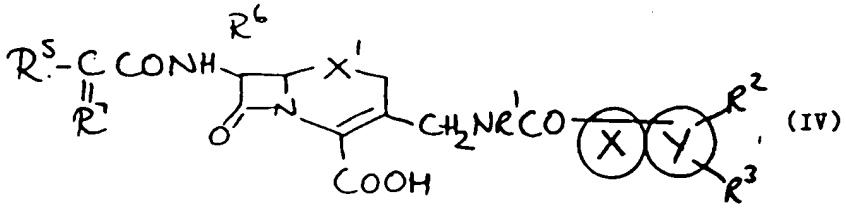
(II)

wherein Q is CH or N and R^4 is hydrogen, C_{1-6}alkyl or C_{1-6}alkoxy.

4. A compound according to claim 1 wherein the cephalosporin compound has a 3-position substituent of the formula (III):

(III)

5. A compound according to any one of claims 1 to 4 of the formula (IV):



(IV)

or a salt or ester thereof wherein R^1, R^2, R^3, X and Y are as defined in any preceding claims; X^1 is sulphur, oxygen, methylene or sulphinyl; R^6 is hydrogen, methoxy or formamido;

R^5 is 2-aminothiazol-4-yl or 2-aminooxazol-4-yl each optionally substituted in the 5-position by fluorine, chlorine or bromine, or R^5 is 5-aminoisothiazol-3- yl, 5-amino-1,2,4-thiadiazol-3-yl, 3-aminopyrazol-5-yl, 3-aminopyrazol-4-yl, 2-aminopyrimidin-5-yl, 2-aminopyrid-6-yl, 4-aminopyrimidin-2-yl, 2-amino-1,3,4-thiadiazol-5-yl or 5-amino-1-methyl-1,2,4-triazol-3-yl;

R^7 is of the formula =N.O.R^8 (having the syn configuration about the double bond) wherein R^8 is hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (1-3C)alkyl(3-6C)cycloalkyl, (3-6C)cycloalkyl(1-3C)alkyl, (3-6C)-alkenyl, optionally substituted by carboxy, (5-8C)cycloalkenyl, (3-6C)alkynyl, (2-5C)alkylcarbamoyl, phenylcarbamoyl, benzylcarbamoyl, (1- 4C)alkylcarbamoyl(1-4C)alkyl, di(1-4C)alkylcarbamoyl(1-4C)-alkyl, (1-4C)haloalkylcarbamoyl(1-4C)alkyl, (1-3C)haloalkyl, (2-6C)hydroxyalkyl, (1-4C)alkoxy(2-4C)alkyl, (1-4C)alkylthio(2-4C)alkyl, (1-4C)alkanesulphinyl(1-4C)alkyl, (1-4C)alkanesulphonyl(1-4C)alkyl, (2-6C)-aminoalkyl, (1-4C)alkylamino(1-6C)alkyl, (2-8C)dialkylamino(2-6C)alkyl, (1-5C)cyanoalkyl, 3-amino-3-carboxypropyl, 2-(amidinothio)ethyl, 2-(N-aminoamidinothio)ethyl, tetrahydropyran-2-yl, thietan-3-yl, 2-oxopyrrolidinyl, or 2-oxotetrahydrofuranyl, or R^8 is of the formula V:-

$$-(CH_2)_q\text{-}C(COOH)=CR^9R^{10} \qquad V$$

wherein q is one or two and R^9 and R^{10} are independently hydrogen or C_{1-4}alkyl; or R^8 is of the formula VI:-

$-CR^{11}R^{12}-(CH_2)_r-COR^{13}$ VI

wherein r is 0-3, R^{11} is hydrogen, (1-3C)alkyl or methylthio, R^{12} is hydrogen, (1-3C)alkyl, (3-7C)-cycloalkyl, cyano, carboxy, (2-5C)carboxyalkyl or methanesulphonylamino, or R^{11} and R^{12} are joined to form, together with the carbon to which they are attached, a (3-7C)carbocyclic ring, and R^{13} is hydroxy, amino, (1-4C)alkoxy, (1-4C)alkylamino or of the formula $NHOR^{14}$ in which R^{14} is hydrogen or (1-4C)-alkyl;

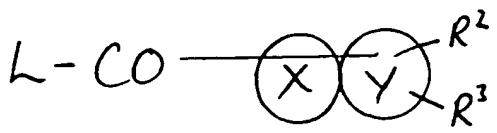
or R^7 may be of the formula $=CH.R^{15}$ wherein R^{15} is hydrogen, halogen, (1-6C)alkyl, (3-7C)-cycloalkyl, (2-6C)alkenyl, (3-7C)cycloalkenyl, phenyl or benzyl.

6. A compound according to claim 5 wherein R^8 is 2-carboxyprop-2-yl.

7. A compound according to claim 1 which is:
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-2-carboxamidomethyl)ceph-3-em-4-carboxylic acid,
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-ethoxyimino)acetamido]-3-(1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-2-carboxamidomethyl)ceph-3-em-4-carboxylic acid,
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino) acetamido-2-(3,4-dihydroxyquinoline-5-carboxamidomethyl)ceph-3-em-4-carboxylic acid,
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(2,3-dihydroxyquinoline-4-carboxamidomethyl)ceph-3-em-4-carboxylic acid, or
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(2,3-dihydroxyquinoline-8-carboxamidomethyl)ceph-3-em-4-carboxylic acid.

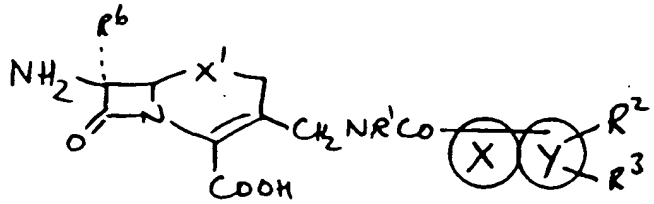
8. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier.

9. A process for preparing a compound according to claim 1 which process comprises:
a) reacting a cephalosporin compound having a 3-position substituent of the formula:
$-CH_2NHR^1$ wherein R^1 is as defined in claim 1 with a compound of the formula VII:



VII

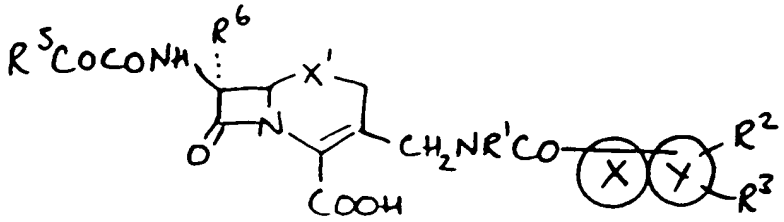
wherein X, Y, R^2 and R^3 are as defined in claim 1 and L is a leaving group; or
b) for compounds of the formula IV, reacting a compound of the formula VIII with a compound of the formula IX or a reactive derivative thereof:



VIII

$R^5-C(=R^7)COOH$ IX

wherein R^1, R^2, R^3, X^1, X, Y, R^5, R^6 and R^7 are as defined in claim 5; or
c) for compounds of the formula IV wherein R^7 is a group $=NOR^8$, reacting a compound of the formula X:



(X)

wherein R^1, R^2, R^3, R^5, R^6, X^1, X and Y are as defined in claim 5, with a compound of the formula: R^8ONH_2 wherein R^8 is as defined in claim 5; or

d) for compounds of the formula IV wherein R^7 is a group $=NOR^8$ and R^8 is other than hydrogen, reacting a compound of the formula IV as hereinbefore defined wherein R^7 is a group $=NOH$ with a compound of the formula XI:

$L^1 - R^{16}$ XI

wherein L^1 is a leaving group and R^{16} is a group R^8 other than hydrogen; or

e) for compounds of the formula IV forming a group R^5 by cyclizing an appropriate precursor thereof:

wherein any functional groups are optionally protected: and thereafter, if necessary:

i) removing any protecting group,

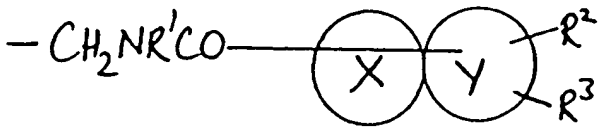
ii) for preparing in vivo hydrolysable esters, esterifying corresponding hydroxy groups,

iii) converting compounds wherein X^1 is S to compounds wherein X^1 is sulphinyl and vice versa,

iv) forming a pharmaceutically acceptable salt.

Patentansprüche

1. Cephalosporin-Verbindung, die in der 3-Stellung einen Substituenten mit der folgenden Formel (I) aufweist:

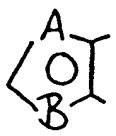


(I)

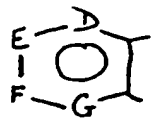
in der:

R^1 für Wasserstoff, C_{1-6}-Alkyl, das gegebenenfalls durch Halogen, Hydroxy, C_{1-4}-Alkoxy, Carboxy, Amino, Cyano, C_{1-6}-Alkanoylamino, Phenyl oder Heteroaryl substituiert ist, steht, oder in der R^1 für C_{2-6}-Alkenyl steht;

X für einen 5- oder 6-gliedrigen Ring steht, der aus der Gruppe mit den Unterformeln a) - b) ausgewählt ist:



a)

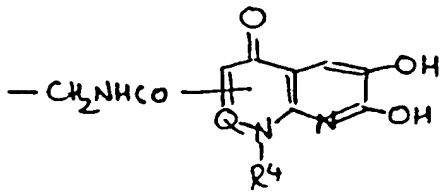


b)

wobei A für CH oder ein Stickstoff-Atom steht; B für Sauerstoff, Schwefel oder eine Gruppe NR^4 steht; keins, eins oder zwei der Symbole D, E, F und G für Stickstoff-Atome stehen und der Rest für CH-Gruppen steht; oder in der X für einen Pyrazinon-, Pyridinon-, Pyridazinon- oder Pyrimidinon-Ring oder für ein Thion-Äquivalent eines derartigen Rings, wobei die Ringe einen Substituenten R^4 an einem Stickstoff-Atom aufweisen, oder für Pyranon oder Pyranthion steht, wobei der Ring X mit zwei beliebigen benachbarten Kohlenstoffatomen an den Ring Y kondensiert ist;
Ring Y für einen ein oder zwei Ring-Stickstoffatome enthaltenden 6-gliedrigen Heteroaryl-Ring steht, der an benachbarten Kohlenstoffatomen durch die Gruppen R^2 und R^3 substituiert ist;
wobei ein Ring des kondensierten X-Y-Ringsystems über ein Kohlenstoffatom mit der Amid-Brücke verbunden ist;
R^2 für Hydroxy oder einen in vivo hydrolysierbaren Ester davon steht;
R^3 ortho zu R^2 steht und für Hydroxy oder einen in vivo hydrolysierbaren Ester davon steht;
wobei R^4 für Wasserstoff, Hydroxy, C_{1-6}-Alkoxy, Phenoxy, C_{2-6}-Alkenyl oder C_{1-6}-Alkyl steht (wobei jede dieser Gruppen gegebenenfalls mit folgendem substituiert ist: Hydroxy, C_{1-6}-Alkoxy, Cyano, Amino, C_{1-6}-Alkylamino, Di-C_{1-6}-alkylamino, Carboxy, C_{1-6}-Alkoxycarbonyl, C_{1-6}-Alkanoyloxy, Carbamoyl, C_{1-6}-Alkylcarbamoyl, Di-C_{1-6}-alkylcarbamoyl, C_{1-6}-Alkoxycarbonylamino, Phenyl, Phenyl-C_{1-6}-alkyl, Carboxyaminocarbonyl, C_{1-6}-Alkoxycarbonylaminocarbonyl, Benzoyl oder C_{3-8}-Cycloalkyl) oder wobei R^4 für Phenyl, C_{3-8}-Cycloalkyl, Amino, C_{1-6}-Alkylamino oder Di-C_{1-6}-alkylamino steht;
wobei das kondensierte X-Y-Ringsystem und/oder jede Phenyl-Gruppe gegebenenfalls mit folgendem substituiert ist: C_{1-6}-Alkyl, Halogen, Hydroxy, Hydroxy-C_{1-6}-alkyl, Cyano, Trifluormethyl, Nitro, Amino, C_{1-6}-Alkylamino, Di-C_{1-6}-alkylamino, C_{1-6}-Alkanoyl, C_{1-6}-Alkoxy, C_{1-6}-Alkylthio, C_{1-6}-Alkanoyloxy, Carbamoyl, C_{1-6}-Alkylcarbamoyl, Di-C_{1-6}-alkylcarbamoyl, Carboxy, Carboxy-C_{1-6}-alkyl, C_{1-6}-Alkoxycarbonyl-C_{1-6}-alkyl, Sulfo, Sulfo-C_{1-6}-alkyl, Sulfonamido-C_{1-6}-alkyl, C_{1-6}-Alkoxycarbonyl, C_{1-6}-Alkanoylamino, Thioureido oder Amidino.

2. Verbindung nach Anspruch 1, wobei R^2 und R^3 beide für Hydroxy stehen.

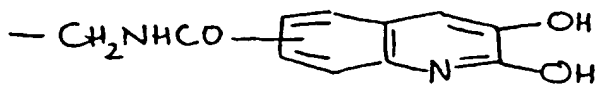
3. Verbindung nach Anspruch 1, wobei die Cephalosporin-Verbindung in der 3-Stellung einen Substituenten mit der folgenden Formel (II) aufweist:



(II)

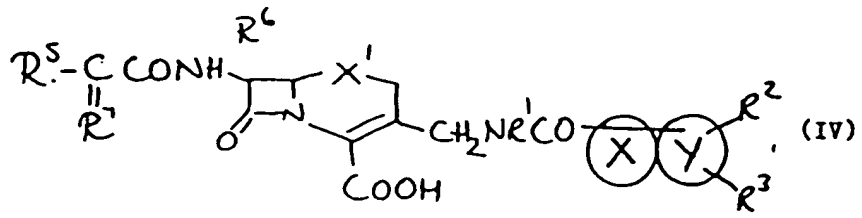
in Q für CH oder N steht und R^4 für Wasserstoff, C_{1-6}-Alkyl oder C_{1-6}-Alkoxy steht.

4. Verbindung nach Anspruch 1, wobei die Cephalosporin-Verbindung in der 3-Stellung einen Substituenten mit der folgenden Formel (III) aufweist:



(III)

5. Verbindung nach einem der Ansprüche 1 bis 4, mit der folgenden Formel (IV):



(IV)

oder ein Salz oder Ester davon, in der
R^1, R^2, R^3 X und Y wie in einem der vorhergehenden Ansprüche definiert sind;
X^1 für Schwefel, Sauerstoff, Methylen oder Sulfinyl steht;
R^6 für Wasserstoff Methoxy oder Formamido steht;
R^5 für 2-Aminothiazol-4-yl oder 2-Aminooxazol-4-yl steht, die jeweils in der 5-Stellung gegebenenfalls durch Fluor, Chlor oder Brom substituiert sind, oder in der R^5 für 5-Aminoisothiazol-3-yl, 5-Amino-1,2,4-thiadiazol-3-yl, 3-Aminopyrazol-5-yl, 3-Aminopyrazol-4-yl, 2-Aminopyrimidin-5-yl, 2-Aminopyrid-6-yl, 4-Aminopyrimidin-2-yl, 2-Amino-1,3,4-thiadiazol-5-yl oder 5-Amino-1-methyl-1,2,4-triazol-3-yl steht;
R^7 für die Formel =N.O.R^8 steht (die an der Doppelbindung die syn-Konfiguration aufweist), wobei R^8 für folgendes steht: Wasserstoff, (1-6C)-Alkyl, (3-8C)Cycloalkyl, (1-3C)Alkyl-(3-6C)cycloalkyl, (3-6C)-Cycloalkyl(1-3C)alkyl, (3-6C)Alkenyl, gegebenenfalls durch Carboxy substituiert, (5-8C)Cycloalkenyl, (3-6C)Alkinyl, (2-5C)Alkylcarbamoyl, Phenylcarbamoyl, Benzylcarbamoyl, (1-4C)Alkylcarbamoyl(1-4C)alkyl, Di(1-4C)alkylcarbamoyl(1-4C)alkyl, (1-4C)Halogenalkylcarbamoyl(1-4C)alkyl, (1-3C)Halogenalkyl, (2-6C)-Hydroxyalkyl, (1-4C)Alkoxy(2-4C)alkyl, (1-4C)Alkylthio(2-4C)alkyl, (1-4C)Alkansulfinyl(1-4C)alkyl, (1-4C)-Alkansulfonyl(1-4C)alkyl, (2-6C)Aminoalkyl, (1-4C)Alkylamino(1-6C)alkyl, (2-8C)Dialkylamino(2-6C)alkyl, (1-5C)Cyanoalkyl, 3-Amino-3-carboxypopyl, 2-(Amidinothio)ethyl, 2-(N-Aminoamidinothio)ethyl, Tetrahydropyran-2-yl, Thietan-3-yl, 2-Oxopyrrolidinyl oder 2-Oxotetrahydrofuranyl, oder wobei R^8 für die folgende Formel V steht:-

$$-(CH_2)_q\text{-}C(COOH) = CR^9R^{10} \qquad V$$

in der q für eins oder zwei steht und R^9 und R^{10} unabhängig für Wasserstoff oder C_{1-4}-Alkyl stehen, oder wobei R^8 für die folgende Formel VI steht:-

$$-CR^{11}R^{12}\text{-}(CH_2)_r\text{-}COR^{13} \qquad VI$$

in der r für 0 - 3 steht, R^{11} für Wasserstoff, (1-3C)Alkyl oder Methylthio steht, R^{12} für Wasserstoff, (1-3C)Alkyl, (3-7C)Cycloalkyl, Cyano, Carboxy, (2-5C)Carboxyalkyl oder Methansulfonylamino steht, oder in der R^{11} und R^{12} zusammen mit dem Kohlenstoff, an den sie gebunden sind, unter Bildung eines (3-7C)carbocyclischen Rings verbunden sind, und in der R^{13} für Hydroxy, Amino, (1-4C)Alkoxy, (1-4C)-Alkylamino oder für die Formel NHOR^{14} steht, in der R^{14} für Wasserstoff oder (1-4C)Alkyl steht;
oder R^7 für die Formel =CH.R^{15} stehen kann, in der R^{15} für Wasserstoff, Halogen, (1-6C)Alkyl, (3-7C)-Cycloalkyl, (2-6C)Alkenyl, (3-7C)Cycloalkenyl, Phenyl oder Benzyl steht.

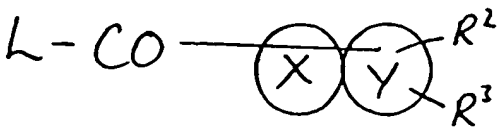
6. Verbindung nach Anspruch 5, wobei R^8 für 2-Carboxyprop-2-yl steht.

7. Verbindung nach Anspruch 1, wobei es sich um folgendes handelt:
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridin-2-carboxamidomethyl)ceph-3-em-4-carbonsäure,
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-ethoxyimino)acetamido]-3-(1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridin-2-carboxamidomethyl)ceph-3-em-4-carbonsäure,
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(3,4-dihydroxychinolin-5-carboxamidomethyl)ceph-3-em-4-carbonsäure,
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(2,3-dihydroxychinolin-4-carboxamidomethyl)ceph-3-em-4-carbonsäure, oder
7-[2-(2-Aminothiazol-4-yl)-2-((Z)-1-carboxy-1-methylethoxyimino)acetamido]-3-(2,3-dihydroxychinolin-8-

carboxamidomethyl)ceph-3-em-4-carbonsäure.

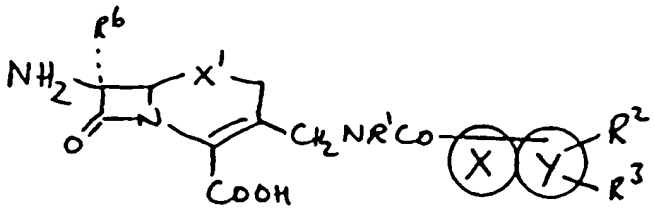
8. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 7 und ein pharmazeutisch geeignetes Trägermittel enthält.

9. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei bei dem Verfahren:
a) eine Cephalosporin-Verbindung, die in der 3-Stellung einen Substituenten mit der Formel: $-CH_2NHR^1$ aufweist, in der R^1 wie in Anspruch 1 definiert ist, mit einer Verbindung mit der Formel VII:



VII

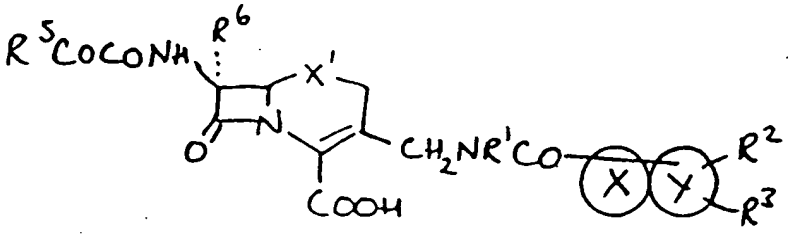
in der X, Y, R^2 und R^3 wie in Anspruch 1 definiert sind und L für eine Austrittsgruppe steht, umgesetzt wird; oder
b) für Verbindungen mit der Formel IV, eine Verbindung mit der Formel VIII mit einer Verbindung mit der Formel IX oder einem reaktiven Derivat davon umgesetzt wird:



VIII

R^5-C(=R^7)COOH IX

wobei R^1, R^2, R^3, X^1, X, Y, R^5, R^6 und R^7 wie in Anspruch 5 definiert sind; oder
c) für Verbindungen mit der Formel IV, bei denen R^7 für die Gruppe =NOR^8 steht, eine Verbindung mit der folgenden Formel X:



(X)

in der R^1, R^2, R^3, R^5, R^6, X^1, X und Y wie in Anspruch 5 definiert sind, mit einer Verbindung mit der Formel: R^8ONH_2 umgesetzt wird, in der R^8 wie in Anspruch 5 definiert ist; oder
d) für Verbindungen mit der Formel IV, bei denen R^7 für die Gruppe =NOR^8 steht und R^8 für etwas anderes als Wasserstoff steht, eine wie oben definierte Verbindung mit der Formel IV, bei der R^7 für die Gruppe =NOH steht, mit einer Verbindung mit der Formel XI umgesetzt wird:

L^1-R^{16} XI

in der L^1 für eine Austrittsgruppe steht und R^{16} für eine Gruppe R^8 steht, bei der es sich nicht um Wasserstoff handelt; oder

e) für Verbindungen mit der Formel IV eine Gruppe R^5 durch Cyclisierung eines geeigneten Vorläufers davon gebildet wird;

wobei alle funktionellen Gruppen gegebenenfalls geschützt sind; und wonach, falls erforderlich,

i) jede Schutzgruppe entfernt wird,

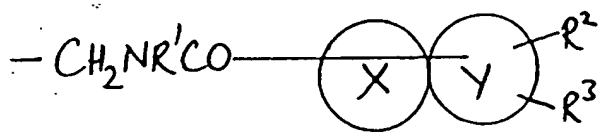
ii) zur Herstellung von in vivo hydrolysierbaren Estern entsprechende Hydroxy-Gruppen verestert werden,

iii) Verbindungen, bei denen X^1 für S steht, in Verbindungen umgewandelt werden, bei denen X^1 für Sulfinyl steht oder umgekehrt,

iv) ein pharmazeutisch geeignetes Salz gebildet wird.

Revendications

1. Céphalosporine portant un substituant en position 3, de formule (I) :

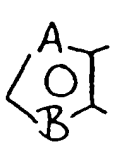


(I)

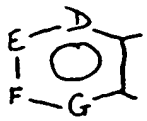
dans laquelle :

R^1 représente l'hydrogène, un groupe alkyle en C_1 à C_6, facultativement substitué avec un groupe halogéno, hydroxy, alkoxy en C_1 à C_4, carboxy, amino, cyano, alcanoylamino en C_1 à C_6, phényle ou hétéroaryle, ou bien R^1 représente un groupe alcényle en C_2 à C_6 ;

X représente un noyau penta- ou hexagonal choisi dans le groupe des sous-formules a) et b) :



a)



b)

dans lesquelles A représente un groupe CH ou un atome d'azote ; B représente l'oxygène, le soufre ou un groupe NR^4 ; zéro, un ou deux de D, E, F et G représentent des atomes d'azote et le reste représente des groupes CH ; ou bien X représente un noyau pyrazinone, pyridinone, pyridazinone ou pyrimidinone, ou est un équivalent thione d'un tel noyau, lesdits noyaux possédant un substitant R^4 sur un atome d'azote, ou bien est un groupe pyranone ou pyranthione ; le noyau X étant condensé par deux quelconques atomes de carbone adjacents avec le noyau Y ;

le noyau Y est un noyau hétéroaryle hexagonal contenant un ou deux atomes d'azote de cycle, substitués sur des atomes de carbone adjacents avec des groupes R^2 et R^3 ;

chaque noyau du système cyclique X-Y condensé étant lié par un atome de carbone à la liaison amide ;

R^2 représente un groupe hydroxy ou un de ses esters hydrolysables in vivo ;

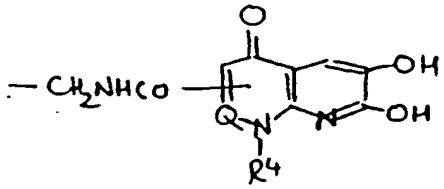
R^3 est en position ortho par rapport à R^2 et représente un groupe hydroxy ou un de ses esters hydrolysables in vivo ;

R^4 représente l'hydrogène, un groupe hydroxy, alkoxy en C_1 à C_6, phénoxy, alcényle en C_2 à C_6 ou alkyle en C_1 à C_6 (n'importe lequel de ces groupes étant facultativement substitué avec un groupe

hydroxy, alkoxy en C_1 à C_6, cyano, amino, alkylamino en C_1 à C_6, di-(alkyle en C_1 à C_6)amino, carboxy, (alkoxy en C_1 à C_6)-carbonyle, alcanoyloxy en C_1 à C_6, carbamoyle, (alkyle en C_1 à C_6)-carbamoyle, di-(alkyle en C_1 à C_6)-carbamoyle, (alkoxy en C_1 à C_6)-carbonylamino, phényle, phényl-(alkyle en C_1 à C_6), carboxyaminocarbonyle, (alkoxy en C_1 à C_6)-carbonylaminocarbonyle, benzoyle ou cycloalkyle en C_3 à C_8), ou bien R^4 représente un groupe phényle, cycloalkyle en C_3 à C_8, amino, alkylamino en C_1 à C_6 ou di-(alkyle en C_1 à C_6)-amino ; le système cyclique X-Y condensé et/ou n'importe quel groupe phényle étant en outre facultativement substitués avec un groupe alkyle en C_1 à C_6, halogéno, hydroxy, hydroxyalkyle en C_1 à C_6, cyano, trifluorométhyle, nitro, amino, alkylamino en C_1 à C_6, di-(alkyle en C_1 à C_6)-amino, alcanoyle en C_1 à C_6, alkoxy en C_1 à C_6, alkylthio en C_1 à C_6, alcanoyloxy en C_1 à C_6, carbamoyle, (alkyle en C_1 à C_6)-carbamoyle, di-(alkyle en C_1 à C_6)-carbamoyle, carboxy, carboxy-(alkyle en C_1 à C_6), (alkoxy en C_1 à C_6)-carbonyl-(alkyle en C_1 à C_6), sulfo, sulfoalkyle en C_1 à C_6, sulfamido, alkyle en C_1 à C_6, (alkoxy en C_1 à C_6)-carbonyle, (alcanoyle en C_1 à C_6)-amino, thiouréido, ou amidino.

2. Composé suivant la revendication 1, dans lequel R^2 et R^3 représentent l'un et l'autre un groupe hydroxy.

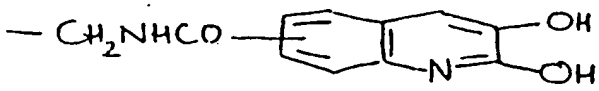
3. Composé suivant la revendication 1, dans lequel la céphalosporine porte un substituant en position 3, de formule (II) :



(II)

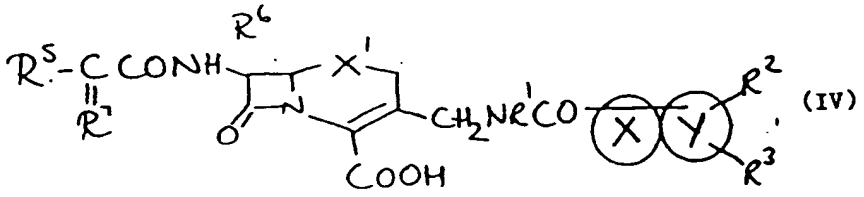
dans laquelle Q représente un groupe CH ou N et R^4 représente l'hydrogène, un groupe alkyle en C_1 à C_6 ou alkoxy en C_1 à C_6.

4. Composé suivant la revendication 1, dans lequel la céphalosporine porte un substituant en position 3, de formule (III) :



(III)

5. Composé suivant l'une quelconque des revendications 1 à 4, de formule (IV) :



(IV)

ou un de ses sels ou esters, formule dans laquelle R^1, R^2, R^3, X et Y répondent aux définitions figurant dans n'importe quelles revendications précédentes ; X^1 représente le soufre, l'oxygène, un groupe méthylène ou sulfinyle ; R^6 représente l'hydrogène, un groupe méthoxy ou formamido ;

R^5 représente un groupe 2-aminothiazole-4-yle ou 2-amino-oxazole-4-yle, chacun facultativement substitué en position 5 avec le fluor, le chlore ou le brome, ou bien R^5 représente un groupe 5-aminoisothiazole-3-yle, 5-amino-1,2,4-thiadiazole-3-yle, 3-aminopyrazole-5-yle, 3-aminopyrazole-4-yle, 2-aminopyrimidine-5-yle, 2-aminopyrid-6-yle, 4-aminopyrimidine-2-yle, 2-amino-1,3,4-thiadiazole-5-yle ou 5-amino-1-méthyl-1,2,4-triazole-3-yle ;

R^7 répond à la formule =N.O.R^8 (possédant la configuration syn de part et d'autre de la double liaison) dans laquelle R^8 représente l'hydrogène, un groupe alkyle en C_1 à C_6, cycloalkyle en C_3 à C_8, (alkyle en C_1 à C_3)-(cycloalkyle en C_3 à C_6), (cycloalkyle en C_3 à C_6)-(alkyle en C_1 à C_3), alcényle en C_3 à C_6, facultativement substitué avec un groupe carboxy, cycloalcényle en C_5 à C_8, alcynyle en C_3 à C_6, (alkyle en C_2 à C_5)-carbamoyle, phénylcarbamoyle, benzylcarbamoyle, (alkyle en C_1 à C_4)-carbamoyl-(alkyle en C_1 à C_4), di-(alkyle en C_1 à C_4)-carbamoyl-(alkyle en C_1 à C_4), (halogénalkyle en C_1 à C_4)-carbamoyl-(alkyle en C_1 à C_4), halogénalkyle en C_1 à C_3, hydroxyalkyle en C_2 à C_6, (alkoxy en C_1 à C_4)-(alkyle en C_2 à C_4), (alkyle en C_1 à C_4)-thio-(alkyle en C_2 à C_4), (alcane en C_1 à C_4)-sulfinyl-(alkyle en C_1 à C_4), (alcane en C_1 à C_4)-sulfonyl-(alkyle en C_1 à C_4), aminoalkyle en C_2 à C_6, (alkyle en C_1 à C_4)-amino-(alkyle en C_1 à C_6), (dialkyle en C_2 à C_8)-amino-(alkyle en C_2 à C_6), cyanalkyle en C_1 à C_5, 3-amino-3-carboxypropyle, 2-(amidinothio)éthyle, 2-(N-aminoamidinothio)éthyle, tétrahydropyranne-2-yle, thiétanne-3-yle, 2-oxopyrrolidinyle ou 2-oxotétrahydrofurannyle, ou bien R^8 répond à la formule V :

$$-(CH_2)_q-C(COOH)=CR^9R^{10} \qquad V$$

dans laquelle q est égal à un ou deux et R^9 et R^{10} réprésentent indépendamment l'hydrogène ou un groupe alkyle en C_1 à C_4 ; ou bien R^8 répond à la formule VI :

$$-CR^{11}R^{12}-(CH_2)_r-COR^{13} \qquad VI$$

dans laquelle r a une valeur de 0 à 3, R^{11} représente l'hydrogène, un groupe alkyle en C_1 à C_3 ou méthylthio, R^{12} représente l'hydrogène, un groupe alkyle en C_1 à C_3, cycloalkyle en C_3 à C_7, cyano, carboxy, carboxyalkyle en C_2 à C_5, ou méthanesulfonylamino ou bien R^{11} et R^{12} sont réunis en formant, en association avec l'atome de carbone auquel ils sont fixés, un noyau carbocyclique en C_3 à C_7, et R^{13} représente un groupe hydroxy, amino, alkoxy en C_1 à C_4, alkylamino en C_1 à C_4 ou bien répond à la formule $NHOR^{14}$ dans laquelle R^{14} représente l'hydrogène ou un groupe alkyle en C_1 à C_4 ;

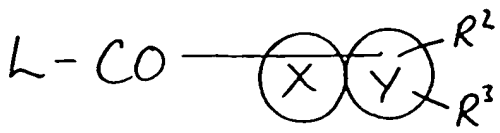
ou bien R^7 peut répondre à la formule =CH.R^{15} dans laquelle R^{15} représente l'hydrogène, un halogène, un groupe alkyle en C_1 à C_6, cycloalkyle en C_3 à C_7, alcényle en C_2 à C_6, cycloalcényle en C_3 à C_7, phényle ou benzyle.

6. Composé suivant la revendication 5, dans lequel R^8 réprésente un groupe 2-carboxyprop-2-yle.

7. Composé suivant la revendication 1, qui est :
l'acide 7-[2-(2-aminothiazole-4-yl)-2-((Z)-1-carboxy-1-méthyléthoxyimino)acétamido]-3-(1-éthyl-1,4-dihydro-4-oxo-1,8-naphtyridine-2-carboxamidométhyl)céph-3-ème-4-carboxylique,
l'acide 7-[2-(2-aminothiazole-4-yl)-2-((Z)-éthoxyimino)acétamido]-3-(1-éthyl-1,4-dihydro-4-oxo-1,8-naphtyridine-2-carboxamidométhyl)céph-3-ème-carboxylique,
l'acide 7-[2-(2-aminothiazole-4-yl)-2-((Z)-1-carboxy-1-méthyléthoxyimino)acétamido-2-(3,4-dihydroxyquinoléine-5-carboxamidométhyl)céph-3-ème-4-carboxylique,
l'acide 7-[2-(2-aminothiazole-4-yl)-2-((Z)-1-carboxy-1-méthyléthoxyimino)acétamido]-3-(2,3-dihydroxy quinoléine-4-carboxamidométhyl)céph-3-ème-4-carboxylique,ou
l'acide 7-[2-(2-aminothiazole-4-yl)-2-((Z)-1-carboxy-1-méthyléthoxyimino)acétamido]-3-(2,3-dihydroxyquinoléine-8-carboxamidométhyl)céph-3-ème-carboxylique.

8. Composition pharmaceutique, qui comprend un composé suivant l'une quelconque des revendications 1 à 7 et un support pharmaceutiquement acceptable.

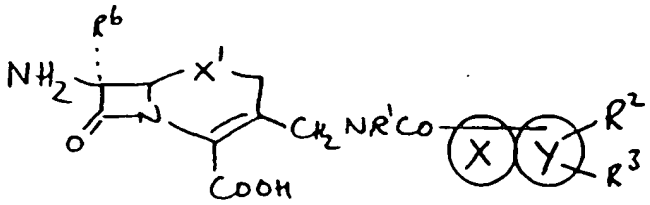
9. Procédé de préparation d'un composé suivant la revendication 1, procédé qui comprend :
a) la réaction d'une céphalosporine portant un substituant en position 3 de formule : $-CH_2NHR^1$ dans laquelle R^1 répond à la définition suivant la revendication 1, avec un composé de formule VII :



VII

dans laquelle X, Y, R^2 et R^3 répondent aux définitions suivant la revendication 1 et L représente un groupe partant : ou

b) pour des composés de formule IV, la réaction d'un composé de formule VIII avec un composé de formule IX ou un de ses dérivés réactifs ;

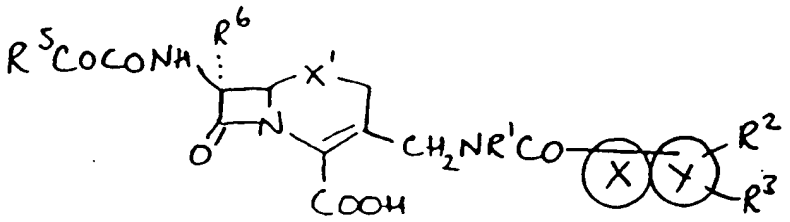


VIII

R^5-C(=R^7)COOH IX

formules dans lesquelles R^1, R^2, R^3, X^1, X, Y, R^5, R^6 et R^7 répondent aux définitions suivant la revendication 5 ; ou

c) pour des composés de formule IV dans laquelle R^7 représente un groupe =NOR^8, la réaction d'un composé de formule X :



(X)

dans laquelle R^1, R^2, R^3, R^5, R^6, X^1, X et Y répondent aux définitions suivant la revendication 5, avec un composé de formule : R^8ONH_2 dans laquelle R^8 répond à la définition suivant la revendication 5 ; ou

d) pour des composés de formule IV dans laquelle R^7 représente un groupe =NOR^8 et R^8 est autre que l'hydrogène, la réaction d'un composé de formule IV répondant à la définition précitée dans laquelle R^7 représente un groupe =NOH avec un composé de formule XI :

L^1 - R^{16} XI

dans laquelle L^1 représente un groupe partant et R^{16} représente un groupe R^8 autre que l'hydrogène ; ou

e) pour des composés de formule IV, la formation d'un groupe R^5 par cyclisation d'un de ses précurseurs appropriés ;

n'importe quels groupes fonctionnels étant facultativement protégé ;

puis, si nécessaire, :

i) l'élimination de n'importe quel groupe protecteur,

ii) pour la préparation d'esters hydrolysables in vitro, l'estérification des groupes hydroxy correspondants,
iii) la transformation de composés dans lesquels X^1 représente S en composés dans lesquels X^1 représente un groupe sulfinyle, et vice versa,
iv) la formation d'un sel pharmaceutiquement acceptable.